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     (FILE 'HOME' ENTERED AT 11:32:30 ON 25 MAY 2005)

     FILE 'EPFULL, FRFULL, GBFULL, PATDPAFULL, PCTFULL, RDISCLOSURE,
     USPATFULL, USPAT2' ENTERED AT 11:33:30 ON 25 MAY 2005
                E CHILTON FLOYD/IN
L1            17 S E4-E9
L2             5 S L1 AND (MARINE OR EPA OR GLA OR BORAGE)

     FILE 'CAPLUS' ENTERED AT 11:40:48 ON 25 MAY 2005
                E CHILTON FLOYD/AU
L3            96 S E4-E9
L4             9 S L3 AND (MARINE OR EPA OR GLA OR BORAGE)
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=> d his

     (FILE 'HOME' ENTERED AT 11:32:30 ON 25 MAY 2005)

     FILE 'EPFULL, FRFULL, GBFULL, PATDPAFULL, PCTFULL, RDISCLOSURE,
     USPATFULL, USPAT2' ENTERED AT 11:33:30 ON 25 MAY 2005
               E CHILTON FLOYD/IN
L1            17 S E4-E9

=> s l1 and (marine or epa or gla or borage)
L2             5 L1 AND (MARINE OR EPA OR GLA OR BORAGE)

=> d ibib 1-5

L2     ANSWER 1 OF 5      PCTFULL   COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER:         2003063793 PCTFULL  ED 20030818  EW 200332
TITLE (ENGLISH):          FATTY ACID-CONTAINING COMPOSITIONS AND METHODS FOR THE
                          TREATMENT OF CYTOKINE MEDIATED DISORDERS
TITLE (FRENCH):           COMPOSITIONS CONTENANT DES ACIDES GRAS ET METHODES POUR
                          LE TRAITEMENT DE TROUBLES MEDIES PAR UNE CYTOKINE
INVENTOR(S):              CHILTON, Floyd, H., 4226 Allistar Road,
                          Winston-Salem, NC 27104, US [US, US];
                          SURETTE, Marc, E., 2344 Westover Drive, Winston-Salem,
                          NC 27103, US [CA, US];
                          KOUMENIS, Iphigenia, L., 3241 York Road, Winston-Salem,
                          NC 27103, US [CY, US];
                          TRAMPOSCH, Kenneth, 8686 Millcreek Drive, E. Amherst,
                          NY 14051, US [US, US]
PATENT ASSIGNEE(S):       PILOT THERAPEUTICS, INC., 2000 Daniel Island Drive,
                          Charleston, SC 29492, US [US, US], for all designates
                          States except US;
                          CHILTON, Floyd, H., 4226 Allistar Road, Winston-Salem,
                          NC 27104, US [US, US], for US only;
                          SURETTE, Marc, E., 2344 Westover Drive, Winston-Salem,
                          NC 27103, US [CA, US], for US only;
                          KOUMENIS, Iphigenia, L., 3241 York Road, Winston-Salem,
                          NC 27103, US [CY, US], for US only;
                          TRAMPOSCH, Kenneth, 8686 Millcreek Drive, E. Amherst,
                          NY 14051, US [US, US], for US only
AGENT:                    HAGAN, Patrick, J.$, Dann, Dorfman, Herrell and
                          Skillman, 1601 Market Street Suite 720, Philadelphia,
                          PA 19103-2307$, US
LANGUAGE OF FILING:       English
LANGUAGE OF PUBL.:        English
DOCUMENT TYPE:            Patent
PATENT INFORMATION:

                          NUMBER              KIND     DATE
                          ---------------------------------
                          WO 2003063793         A2 20030807
DESIGNATED STATES
       W:                 AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR
                          CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID
                          IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD
                          MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG
                          SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
       RW (ARIPO):        GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW
       RW (EAPO):         AM AZ BY KG KZ MD RU TJ TM
       RW (EPO):          AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU
                          MC NL PT SE SI SK TR
       RW (OAPI):         BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
APPLICATION INFO.:        WO 2003-US2954         A  20030131
PRIORITY INFO.:           US 2002-10/066,334        20020131  abandoned

L2     ANSWER 2 OF 5      PCTFULL   COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER:         2000059303 PCTFULL  ED 20020515
TITLE (ENGLISH):          OXIDIZED POLYUNSATURATED FATTY ACIDS HAVING
                          ANTI-PROLIFERATIVE ACTIVITY AND METHODS OF USE
TITLE (FRENCH):           ACIDES GRAS POLY-INSATURES OXYDES POSSEDANT UNE
```

ACTIVITE ANTIPROLIFERATIVE ET PROCEDES D'UTILISATION

INVENTOR(S): **CHILTON, Floyd, H.**
PATENT ASSIGNEE(S): WAKE FOREST UNIVERSITY;
CHILTON, Floyd, H.
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2000059303	A1	20001012

DESIGNATED STATES
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW GH GM KE LS MW SD SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG
APPLICATION INFO.: WO 2000-US9030 A 20000405
PRIORITY INFO.: US 1999-09/286,180 19990405

abandoned

L2 ANSWER 3 OF 5 PCTFULL COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER: 1999042101 PCTFULL ED 20020515
TITLE (ENGLISH): DIETARY CONTROL OF ARACHIDONIC ACID METABOLISM
TITLE (FRENCH): REGULATION DIETETIQUE DU METABOLISME DE L'ACIDE ARACHIDONIQUE
INVENTOR(S): **CHILTON, Floyd, H.**
PATENT ASSIGNEE(S): WAKE FOREST UNIVERSITY;
CHILTON, Floyd, H.
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9942101	A1	19990826

DESIGNATED STATES
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW GH GM KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG
APPLICATION INFO.: WO 1999-US3120 A 19990212
PRIORITY INFO.: US 1998-09/028,256 19980223

US 6,107,334

L2 ANSWER 4 OF 5 USPATFULL on STN
ACCESSION NUMBER: 2002:330338 USPATFULL
TITLE: Fatty acid-containing emulsion with increased bioavailability
INVENTOR(S): **Chilton, Floyd H.**, Winston-Salem, NC, UNITED STATES
Surette, Marc E., Winston-Salem, NC, UNITED STATES
Koumenis, Iphigenia L., Winston-Salem, NC, UNITED STATES

NUMBER	KIND	DATE
PATENT INFORMATION: US 2002188024	A1	20021212
APPLICATION INFO.: US 2002-66334	A1	20020131 (10)

instant case

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2000-644380, filed on 23 Aug 2000, PENDING A 371 of International Ser. No. WO 1999-US3120, filed on 12 Feb 1999, UNKNOWN A 371 of International Ser. No. US 1998-28256, filed on 23 Feb 1998, GRANTED, Pat. No. US 6107334
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: DANN DORFMAN HERRELL & SKILLMAN, SUITE 720, 1601 MARKET STREET, PHILADELPHIA, PA, 19103-2307
NUMBER OF CLAIMS: 32
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 21 Drawing Page(s)
LINE COUNT: 2981
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 5 OF 5 USPATFULL on STN
ACCESSION NUMBER: 2000:109839 USPATFULL
TITLE: Dietary control of arachidonic acid metabolism
INVENTOR(S): **Chilton, Floyd H.**, Pilot Mountain, NC, United States
PATENT ASSIGNEE(S): Wake Forest University, Winston-Salem, NC, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6107334		20000822
APPLICATION INFO.:	US 1998-28256		19980223 (9)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Jordan, Kimberly
LEGAL REPRESENTATIVE: Corder, Timothy S.Vinson & Elkins LLP
NUMBER OF CLAIMS: 11
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 17 Drawing Figure(s); 10 Drawing Page(s)
LINE COUNT: 2249
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

(BORAGE OR BORAGES)
L4 9 L3 AND (MARINE OR EPA OR GLA OR BORAGE)

=> d ibib abs 1-9

L4 ANSWER 1 OF 9 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:478703 CAPLUS
DOCUMENT NUMBER: 141:224574
TITLE: Dietary Echium oil increases plasma and neutrophil long-chain (n-3) fatty acids and lowers serum triacylglycerols in hypertriglyceridemic humans
AUTHOR(S): Surette, Marc E.; Edens, Michelle; **Chilton, Floyd H.**; Tramposch, Kenneth M.
CORPORATE SOURCE: Pilot Therapeutics Incorporated, Charleston, SC, 29492, USA
SOURCE: Journal of Nutrition (2004), 134(6), 1406-1411
CODEN: JONUAI; ISSN: 0022-3166
PUBLISHER: American Society for Nutritional Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Consumption of fish or fish oils containing long-chain n-3 polyunsatd. fatty acids (PUFA), such as eicosapentaenoic acid (**EPA**, C20:5n-3) and docosahexaenoic acid (DHA, C22:6n-3), is associated with cardiovascular benefits, including decreased blood triacylglycerol concns. and decreased mortality from coronary heart disease. Shorter-chain dietary n-3 PUFA, such as α-linolenic acid (C18:3n-3), from vegetable oils are inefficiently converted to **EPA** and DHA and do not have the hypotriglyceridemic properties attributed to fish oils. This study examined the effects of dietary Echium oil, a plant oil containing stearidonic acid (C18:4n-3), on tissue fatty acid contents and blood serum triacylglycerol concns. in asymptomatic humans with mild-to-moderate hypertriglyceridemia. They underwent 4-wk lead-in period and then were instructed to follow the National Cholesterol Education Program Step 1 diet. Subjects (n = 11) whose blood serum triacylglycerol concns. remained between 3.4 and 5.1 mmol/L (300 and 450 mg/dL) were instructed to consume 15 g Echium oil daily for 4 wk. During the treatment period, blood serum triacylglycerol concns. decreased by 21% (0.87±0.26 mmol/L) compared with baseline; 8 of the 11 subjects had decreases in serum triacylglycerol levels 13-52% with average decrease from baseline of 30% (1.26±0.41 mmol/L). There were no significant changes in any other clin. laboratory variables. The concns. of long-chain n-3 PUFA, including **EPA**, were increased in blood plasma and neutrophils of the subjects consuming the Echium oil. Thus, dietary plant oils rich in stearidonic acid are metabolized to longer-chain and more unsatd. n-3 PUFA. These oils appear to possess hypotriglyceridemic properties typically associated with fish oils.
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:358588 CAPLUS
DOCUMENT NUMBER: 139:337360
TITLE: Inhibition of leukotriene biosynthesis by a novel dietary fatty acid formulation in patients with atopic asthma: a randomized, placebo-controlled, parallel-group, prospective trial
AUTHOR(S): Surette, Marc E.; Koumenis, Iphigenia L.; Edens, Michelle B.; Tramposch, Kenneth M.; Clayton, Bert; Bowton, David; **Chilton, Floyd H.**
CORPORATE SOURCE: Department of Research and Development, Pilot Therapeutics Inc., Charleston, SC, USA
SOURCE: Clinical Therapeutics (2003), 25(3), 972-979
CODEN: CLTHDG; ISSN: 0149-2918
PUBLISHER: Excerpta Medica, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Background: Leukotriene inhibitors and leukotriene-receptor antagonists are effective in the treatment of inflammatory diseases such as asthma. A search of the entirety of MEDLINE using the terms diet plus leukotrienes

identified numerous studies that have explored dietary-management strategies to reduce leukotriene levels through supplementation with polyunsatd. fatty acids such as gamma-linolenic acid (**GLA**) and eicosapentaenoic acid (**EPA**). However, the search found no studies on the use of combinations of these fatty acids in patients with asthma. Objective: The goal of this study was to determine the effect of daily intake of an emulsion (PLT 3514) containing dietary **GLA** and **EPA** on ex vivo stimulated whole blood leukotriene biosynthesis in patients with atopic asthma. Methods: This was a randomized, double-blind, placebo-controlled, parallel-group, prospective trial in patients with mild to moderate atopic asthma. Patients consumed 10 g PLT 3514 emulsion (containing 0.75 g **GLA** + 0.5 g **EPA**), 15 g PLT 3514 emulsion (containing 1.13 g **GLA** + 0.75 g **EPA**), or placebo (olive oil) emulsion daily for 4 wk. Plasma fatty acids were measured by gas chromatog., and stimulated whole blood leukotrienes were measured by reverse-phase high-performance liquid chromatog. with UV detection using a diode array detector. Results: Forty-three patients (33 women, 10 men) participated in the study. Leukotriene biosynthesis was significantly decreased in patients consuming 10 or 5 g PLT 3514 compared with placebo ($P < 0.05$, anal. of covariance). No clin. significant changes in vital signs were observed throughout the study, and here were no significant between-group differences in treatment-emergent adverse events or mean clin. laboratory values. Conclusion: Daily consumption of dietary **GLA** and **EPA** in a novel emulsion formulation inhibited leukotriene biosynthesis in this population of patients with atopic asthma and was well tolerated.

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 9 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:358587 CAPLUS

DOCUMENT NUMBER: 139:100398

TITLE: Inhibition of leukotriene synthesis, pharmacokinetics, and tolerability of a novel dietary fatty acid formulation in healthy adult subjects

AUTHOR(S): Surette, Marc E.; Koumenis, Iphigenia L.; Edens, Michelle B.; Tramposch, Kenneth M.; **Chilton, Floyd H.**

CORPORATE SOURCE: Department of Research and Development, Pilot Therapeutics Inc., Charleston, SC, USA

SOURCE: Clinical Therapeutics (2003), 25(3), 948-971
CODEN: CLTHDG; ISSN: 0149-2918

PUBLISHER: Excerpta Medica, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Background: Numerous studies have explored dietary-management strategies for decreasing leukotriene synthesis by inflammatory cells through supplementation with polyunsatd. fatty acids such as gamma-linolenic acid (**GLA**) and eicosapentaenoic acid (**EPA**). Objectives: This study sought to determine the optimal daily intake, ratios, and formulation of dietary **GLA** and **EPA** required to safely reduce leukotriene biosynthesis in healthy individuals, and to evaluate the pharmacokinetics and safety profile of such a formulation. Methods: Two preliminary trials were conducted to determine the min. effective levels of **GLA** and **EPA** intake needed to reduce leukotriene biosynthesis and prevent increases in plasma arachidonic acid (AA) concns. These preliminary trials were followed by a single-center, randomized, double-blind, placebo-controlled, parallel-group, escalating-intake inpatient trial of a dietary **GLA**/**EPA** emulsion (PLT 3514) in healthy adult subjects. Subjects consumed either 10, 20, or 100 g of the PLT 3514 emulsion (resp. containing 0.75 g **GLA** + 0.5 g **EPA**, 1.5 g **GLA** + 1 g **EPA**, and 7.5 g **GLA** + 5 g **EPA**), or a placebo emulsion containing olive oil daily for 14 days. Plasma fatty acids were measured by gas chromatog. Stimulated whole blood leukotrienes were measured by high-performance liquid chromatog. with UV detection. Results: Thirty subjects were included in the preliminary trials; 47 subjects were enrolled in the escalating-intake trial, of whom 42 completed the study. In the preliminary trials, intake

of **GLA** 1.5 g/d in gelatin capsules decreased the capacity to synthesize leukotrienes but increased plasma levels of AA (both, $P < 0.05$). Inclusion of 0.25 or 1 g of dietary **EPA** prevented the increase in plasma AA concns. Dietary **GLA** and **EPA** showed significantly enhanced bioavailability when consumed in 20 g PLT 3514 emulsion compared with consumption in gelatin capsules ($P < 0.05$), resulting in a reduction in the amount of intake required to block leukotriene biosynthesis. Pharmacokinetic analyses indicated that fasting plasma **GLA** and **EPA** levels plateaued within 7 days' daily consumption at all levels of intake, whereas the time to maximum plasma concentration (Tmax) was shorter for **GLA** than for **EPA**. The Tmax was similar on days 1 and 14 for both **GLA** and **EPA**. There were no clin. significant between-group differences in changes in vital signs, mean clin. laboratory values, or abbreviated hematol. laboratory tests, or significant differences in the occurrence of treatment-emergent adverse events between the group consuming up to 20 g/d of the **GLA**/**EPA** emulsion and the group consuming placebo. Conclusion: Consumption of specific proportions and intake levels of dietary **GLA** and **EPA** in a novel emulsion formulation inhibited leukotriene biosynthesis and appeared to be well tolerated in this population of healthy adult subjects.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:947015 CAPLUS
DOCUMENT NUMBER: 138:16642
TITLE: Fatty acid-containing emulsion with increased bioavailability
INVENTOR(S): **Chilton, Floyd H.**; Surette, Marc E.; Koumenis, Iphigenia L.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 50 pp., Cont.-in-part of U.S. Ser. No. 644,380.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002188024	A1	20021212	US 2002-66334	20020131
US 6107334	A	20000822	US 1998-28256	19980223
WO 9942101	A1	19990826	WO 1999-US3120	19990212
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
WO 2003063793	A2	20030807	WO 2003-US2954	20030131
WO 2003063793	A3	20031106		
WO 2003063793	B1	20040219		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.: US 1998-28256 W 19980223
WO 1999-US3120 W 19990212

US 2000-644380 A2 20000823
US 2002-66334 A 20020131

AB Compns. for the treatment of symptoms of inflammatory disorders may include γ-linolenic acid or dihomo-γ-linolenic acid, an inhibitor of Δ5-desaturase, and optionally stearidonic acid or ω-3 arachidonic acid. Preferred formulations may be in the form of a good tasting, preferably milk or fruit-based drink, or a dried powder. Compns. reduce inflammation and inhibit increase in serum arachidonic acid associated with γ-linolenic acid. For example, a stabilized emulsion that can be consumed neat or easily mixed in a drink or yogurt contained (by weight) **borage** oil 21.00%, **marine** oil 16.5%, lecithin 0.50%, flavor and flavor masking agent 2.00%, colorant 0.05%, ascorbyl palmitate 0.20%, sorbic acid 0.16%, sucrose 25.00%, xanthan gum 0.3%, water 29.29%, and glycerin 5.00%. The composition is packaged in an oxygen-free environment in single daily dosage packages made of oxygen impermeable materials. The recommended daily dosage of 20 g/day would deliver about 1.5 g of γ-linolenic acid and about 1.0 g of eicosapentaenoic acid per day.

L4 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:539297 CAPLUS
DOCUMENT NUMBER: 134:162330
TITLE: Addition of eicosapentaenoic acid to γ-linolenic acid-supplemented diets prevents serum arachidonic acid accumulation in humans
AUTHOR(S): Barham, J. Brooke; Edens, Michelle B.; Fonteh, Alfred N.; Johnson, Margaret M.; Easter, Linda; **Chilton, Floyd H.**
CORPORATE SOURCE: Department of Internal Medicine (Section on Pulmonary and Critical Care Medicine), Wake Forest University School of Medicine, Winston-Salem, NC, 27157, USA
SOURCE: Journal of Nutrition (2000), 130(8), 1925-1931
CODEN: JONUAI; ISSN: 0022-3166
PUBLISHER: American Society for Nutritional Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The objective of this study was to design a supplementation strategy that maintained the capacity of γ-linolenic acid (**GLA**) to reduce lipid mediators without causing elevations in serum arachidonate (AA) levels. Initial in vitro studies utilizing HEP-G2 liver cells revealed that addition of eicosapentaenoic acid (**EPA**) blocked Δ-5-desaturase activity, the terminal enzymic step in AA synthesis. To test the in vivo effects of a **GLA** and **EPA** combination in humans, adult volunteers consuming controlled diets supplemented these diets with 3.0 g/d of **GLA** and **EPA**. This supplementation strategy significantly increased serum levels of **EPA**, but did not increase AA levels. **EPA** and the elongation product of **GLA**, dihomo-γ-linolenic acid (DGLA) levels in neutrophil glycerolipids increased significantly during the 3-wk supplementation period. Neutrophils isolated from volunteers fed diets supplemented with **GLA** and **EPA** released similar quantities of AA, but synthesized significantly lower quantities of leukotrienes compared with their neutrophils before supplementation. This study revealed that a **GLA** and **EPA** supplement combination may be utilized to reduce the synthesis of proinflammatory AA metabolites, and importantly, not induce potentially harmful increases in serum AA levels.

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:510309 CAPLUS
DOCUMENT NUMBER: 127:204948
TITLE: Dietary supplementation with γ-linolenic acid alters fatty acid content and eicosanoid production in healthy humans
AUTHOR(S): Johnson, Margaret M.; Swan, Dennis D.; Surette, Marc E.; Stegner, Jane; Chilton, Tanya; Fonteh, Alfred N.;

Chilton, Floyd H.
CORPORATE SOURCE: Department Internal Medicine, Section Pulmonary and Critical Care Medicine, Bowman Gray School Medicine of Wake Forest University, Winston-Salem, NC, 27157-1054, USA
SOURCE: Journal of Nutrition (1997), 127(8), 1435-1444
CODEN: JONUAI; ISSN: 0022-3166
PUBLISHER: American Society for Nutritional Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To understand the in vivo metabolism of dietary γ-linolenic acid (**GLA**), we supplemented the diets of 29 volunteers with **GLA** in doses of 1.5-6.0 g/d. Twenty-four subjects ate controlled eucaloric diets consisting of 25% fat; the ramining subjects maintained their typical Western diets. **GLA** and dihomo-γ-linolenic acid (DGLA) increased in serum lipids of subjects supplemented with 3.0 and 6.0 g/d; serum arachidonic acid increased in all subjects. **GLA** supplementation with 3.0 and 6.0 g/d also resulted in an enrichment of DGLA in neutrophil phospholipids but no change in **GLA** or AA levels. Before supplementation, DGLA was associated primarily with phosphatidylethanolamine (PE) of neutrophil glycerolipids, and DGLA increased significantly in PE and neutral lipids after **GLA** supplementation. Extending the supplementation to 12 wk did not consistently change the magnitude of increase in either serum or neutrophil lipids in subjects receiving 3.0 g/d. After **GLA** supplementation, A23187-stimulated neutrophils released significantly more DGLA, but AA release did not change. Neutrophils obtained from subjects after 3 wk of supplementation with 3.0 g/d **GLA** synthesized less leukotriene B4 ($P < 0.05$) and platelet-activating factor. Together, these data reveal that DGLA, the elongase product of **GLA**, but not AA accumulates in neutrophil glycerolipids after **GLA** supplementation. The increase in DGLA relative to AA within inflammatory cells such as the neutrophil may attenuate the biosynthesis of AA metabolites and may represent a mechanism by which dietary **GLA** exerts an anti-inflammatory effect.

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:223182 CAPLUS
DOCUMENT NUMBER: 124:286939
TITLE: Metabolism of gammalinolenic acid in human neutrophils
AUTHOR(S): Chilton-Lopez, Tanya; Surette, Marc E.; Swan, Dennis D.; Fonteh, Alfred N.; Johnson, Margaret M.; **Chilton, Floyd H.**
CORPORATE SOURCE: Dep. Internal Med., Gray Sch. Med. Wake Forest Univ., Winston-Salem, NC, 27157, USA
SOURCE: Journal of Immunology (1996), 156(8), 2941-7
CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER: American Association of Immunologists
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Gammalinolenic acid (**GLA**), when provided as a dietary supplement, has been reported to improve clin. symptoms of several inflammatory disorders. The goal of the current study was to examine the metabolism of **GLA** and its relationship to arachidonic acid (AA) in the human neutrophil. Initial studies indicated that neutrophils provided **GLA** in vitro rapidly elongate it (by two carbons) to dihomogammalinolenic acid (DGLA). The bulk of this newly formed DGLA is incorporated into neutral lipids and specifically triacylglycerides. Neutrophils from volunteers supplemented with **GLA** as **borage** oil also had elevated quantities of DGLA but not **GLA**, when compared with neutrophils from volunteers not consuming the **GLA** supplement. To determine whether DGLA could be mobilized from cellular glycerolipids, neutrophils were stimulated with ionophore A23187 and fatty acid levels were determined DGLA and AA were both released during stimulation, and the quantities of DGLA mobilized increased threefold after in vitro **GLA** supplementation. Exogenously

provided DGLA was converted to one major metabolite during cell stimulation; this product migrated on reverse-phase HPLC with the 15-lipoxygenase product, 15-hydroxy-eicosatrienoic acid (15-HETre). Both 15-HETre and DGLA (provided exogenously) inhibited the formation of leukotriene B4 (LTB4) and 20-hydroxy-leukotriene B4 (20-OH-LTB4). The IC50 for 15-HETre inhibition of both LTB4 and 20-OH-LTB4 in A23187-stimulated neutrophils was 5 μM. This inhibition could be reversed by removing the compds. from the cells. Taken together, these data reveal that there are enzymes within the human neutrophil that metabolize **GLA** or its elongation product DGLA, and that the metabolism of **GLA** and AA may interact at a number of critical junctures.

L4 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:100989 CAPLUS
DOCUMENT NUMBER: 118:100989
TITLE: Dietary n-3 fatty acid effects on neutrophil lipid composition and mediator production: influence of duration and dosage
AUTHOR(S): **Chilton, Floyd H.**; Patel, Manish; Fonteh, Alfred N.; Hubbard, Walter C.; Triggiani, Massimo
CORPORATE SOURCE: Bowman Gray Sch. Med., Wake Forest Univ., Winston-Salem, NC, 27157, USA
SOURCE: Journal of Clinical Investigation (1993), 91(1), 115-22
CODEN: JCINAO; ISSN: 0021-9738
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Healthy volunteers supplemented their usual Western diets with Promega fish oil supplement (eicosapentaenoic acid [**EPA**] 0.28 g, docosahexaenoic acid [DCHA] 0.12 g, other n-3 fatty acids 0.10 g/capsule) using 3 protocols. Initial expts. (protocols 1 and 2) investigated the kinetics of incorporation of n-3 fatty acids into serum and neutrophil lipids after 10 capsules/day of Promega. **EPA** was rapidly detected in both serum and neutrophil lipids; the arachidonic acid (AA) to **EPA** ratio in neutrophil phospholipids showed a maximum reduction of 49:1 to 8:1 within 1 wk of beginning supplementation. **EPA** was preferentially incorporated into phosphatidylethanolamine and phosphatidylcholine, but not phosphatidylinositol. Long-term supplementation for ≤7 wk did not influence the AA/ **EPA** ratio or the distribution of **EPA** among neutrophil phospholipids in a manner that was not observed after the 1st wk. Neutrophils produced similar quantities of platelet-activating factor and slightly lower quantities of leukotriene B4 during long-term supplementation when compared with presupplementation values. Expts. examining the influence of Promega dosage indicated that the AA/**EPA** ratio in neutrophil lipids decreased in a dose-dependent manner. Only when the dose was increased to 15 capsules/day was there a reduction in the AA/DCHA ratio in neutrophil lipids. The quantity of AA in neutrophil lipids remained relatively constant at all supplement doses. Taken together, the current study demonstrates the capacity of n-3 fatty acids provided with a Western diet to be rapidly incorporated into neutrophil lipids. However, dietary n-3 fatty acids appear not to significantly reduce arachidonate content in neutrophil phospholipids. Constant arachidonate levels may account for the lack of large redns. in the biosynthesis of lipid mediators by neutrophils after fish-oil supplementation.

L4 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1990:629492 CAPLUS
DOCUMENT NUMBER: 113:229492
TITLE: Evidence that increasing the cellular content of eicosapentaenoic acid does not reduce the biosynthesis of platelet-activating factor
AUTHOR(S): Triggiani, Massimo; Connell, Theresa R.; **Chilton, Floyd H.**
CORPORATE SOURCE: Sch. Med., Johns Hopkins Univ., Baltimore, MD, 21224, USA
SOURCE: Journal of Immunology (1990), 145(7), 2241-8
CODEN: JOIMA3; ISSN: 0022-1767

DOCUMENT TYPE: Journal
LANGUAGE: English

AB Platelet-activating factor (PAF) biosynthesis was examined in neutrophils from individuals on a fish oil-enriched diet and in mast cells enriched with eicosapentaenoic acid (**EPA**) in vitro. Neutrophils isolated from males who were fed fish oil supplement (**EPA**; 2.8 g/day) for 5 wk contained large quantities of eicosapentaenoate in phosphatidylcholine (PC) and phosphatidylethanolamine and less in phosphatidylinositol. The ratio arachidonate/eicosapentaenoate in PC and phosphatidylethanolamine decreased from >10 before the enriched diet to approx. 3 after the diet. The putative precursor of PAF, 1-O-alkyl-2-acyl-sn-glycero-3-phosphocholine (1-O-alkyl-2-acyl-GPC) contained the bulk of eicosapentaenoate in PC subclasses with smaller quantities found in 1-acyl and 1-alk-1'-enyl linked species. Ionophore A23187-stimulated neutrophils produced similar quantities of PAF before and after enriched diet. Neutrophils during normal diet acylated 1-O-alkyl-2-lyso-GPC only with arachidonate whereas neutrophils from individuals on enriched diet transferred both arachidonate and eicosapentaenoate into exogenously-provided 1-O-alkyl-2-lyso-GPC. This allowed for the labeling of neutrophils with 1-O-[3H]-alkyl-2-arachidonoyl-GPC (before diet) as well as neutrophils with 1-O-[3H]-alkyl-2-eicosapentaenoyl-GPC and 1-O-[3H]-alkyl-2-arachidonoyl-GPC (after diet). Neutrophils after diet converted similar quantities of these labeled precursors to labeled PAF upon stimulation as those before the diet. Anal. of the nature of the long chain acyl residue remaining in the sn-2 position of 1-alkyl-2-acyl-GPC after cell stimulation indicated that arachidonate and eicosapentaenoate were both released from 1-O-alkyl-2-acyl-GPC at comparable rates. In vitro supplementation of murine mast cells (PT-18) with arachidonic acid or **EPA** caused a marked increase in the amount of PAF produced by the cell without having any effect on histamine release. Data from these expts. suggest that **EPA** is incorporated into a PAF precursor pool. However, this appears not to inhibit PAF production because phospholipase A2 can use eicosapentaenoate- as well as arachidonate-containing phospholipids in the initial step of PAF biosynthesis.